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A systematic review and meta-analysis of interventions to induce attempts to quit tobacco among adults not ready to quit

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ABSTRACT (words=250/250)

The prevalence of past year smoking cessation remains below 10% in the US. Most who smoke are not ready to quit in the near future. Cessation requires both 1) initiating a quit attempt (QA) and 2) maintaining abstinence. Most research has focused on abstinence among people already motivated to quit. We systematically reviewed interventions to promote QAs among people not motivated to quit tobacco. We searched PubMed, CENTRAL, PsycINFO, Embase, and our personal libraries for randomized trials of tobacco interventions that reported QAs as an outcome among adults not ready to quit. We screened studies and extracted data in duplicate. We pooled findings of the 25 included studies using Mantel-Haenszel random effects meta-analyses when ≥2 studies tested the same intervention. Most (24) trials addressed cigarettes and one addressed smokeless tobacco. Substantial heterogeneity among trials resulted in a series of small meta-analyses. Findings indicate varenicline may increase QAs more than no varenicline (n=320; RR=1.4, 95% CI=1.1 to 1.7; I^2=0%) and nicotine replacement therapy (NRT) may increase QAs more than no NRT (n=2,568; RR=1.1, 95% CI=1.02 to 1.3; I^2=0%). Pooled effects for motivational counseling, reduction counseling, and very low nicotine content cigarettes showed no clear evidence of benefit or harm. The evidence was judged to be of medium to very low certainty due to imprecision, inconsistency, and risk of bias, suggesting that further research is likely to change interpretation of our results. Findings de monstrate the need for more high-quality research on interventions to induce QAs among adults not ready to quit tobacco.

Public Significance Statement

Most people who use tobacco do not plan to quit in the near future and thus interventions to induce quit attempts are needed. This systematic review demonstrates that people who are unmotivated to quit smoking can benefit from treatment and found varenicline and nicotine replacement therapy are particularly promising interventions. However, evidence was insufficient to conclusively support or refute the effectiveness of any single modality and thus further research is needed.

Key Words: Cigarette smoking; Quit attempt; Tobacco treatment; Smoking cessation; Tobacco use cessation.

Introduction

Tobacco use is associated with over 7 million deaths per year worldwide (WHO, 2017) and is a leading cause of preventable death (Murray et al., 2020). In the United States, cigarette smoking is the most common form of tobacco use (Cornelius et al., 2020) and the prevalence of past year smoking cessation remains below 10% (Creamer et al., 2019). Most people who smoke are not ready (i.e., unwilling, unmotivated, or unable) to quit at any given point in time (Reid et al., 2019). Further, the prevalence of past year quit attempts (QA) is approximately 55% (Babb et al., 2017). Successful cessation requires both 1) initiating a QA and 2) maintaining abstinence. Most intervention research is focused on the latter yet increasing the prevalence of QAs is another way to increase cessation and decrease tobacco related death and disease. In this review, we systematically review the research on interventions to promote QAs among people not ready to quit tobacco.

Smoking cessation is often a long process involving fluctuations in readiness to quit (Hughes et al., 2013), many QAs (Chaiton et al., 2016), and evolving goals, challenges, and opportunities (Baker et al., 2011; Fiore et al., 2000; Schlam & Baker, 2013). The Phase-Based Model suggests that tobacco treatment should address "phase-specific" barriers to cessation (Baker et al., 2011), meaning treatment goals should match tobacco users' readiness to quit. For example, prior research within this framework demonstrates people in the "Motivation Phase" (i.e., those not ready to quit) benefit from interventions to promote the initiation of a QA (Schlam & Baker, 2013). Similarly, the Transtheoretical Model of Change identifies the importance of interventions to promote movement from one stage of change (e.g., pre-contemplation) to the next (e.g., contemplation) in the process of tobacco cessation (Prochaska & DiClemente, 1983). More recent research demonstrates the fluidity of motivation and intention to quit tobacco. For example, in a series of naturalistic studies, most adults who smoked cigarettes frequently transitioned between intention to quit, no intention to quit, and smoking as usual (Hughes et al., 2013; Hughes et al., 2005; Peters & Hughes, 2009). Among those initially not ready to

quit, increases in motivation to quit during treatment appear to be associated with increased likelihood of QAs and successful cessation (Jardin & Carpenter, 2012; Klemperer et al., 2020).

Recent guidelines recommend that all smokers are offered pharmacological and behavioral cessation treatment, regardless of their motivation to quit (NICE, 2021; Krist et al., 2021). Multiple interventions have been developed to promote cessation among people not ready to quit at baseline (Carpenter et al., 2004; Cook et al., 2016). For example, motivational interviewing is a widely used treatment intended for people unmotivated to change (Miller & Rollnick, 2012), and a brief motivation-based intervention (i.e., "The 5Rs") is recommended by the US Public Health Service for people not ready to quit smoking (Fiore, 2008). The effectiveness of these and other *cessation induction* strategies (i.e., methods to increase QAs) is not entirely clear. A recent Cochrane review could not determine the effectiveness of motivational interviewing for smoking cessation, partly due to inconsistencies between studies (Lindson, Thompson, et al., 2019), but also because most of the included studies recruited participants already deemed motivated to quit at baseline. This suggests that motivational interventions for smoking are often tested outside of the target population and demonstrates a paucity of research examining interventions for those not motivated to quit.

Reducing cigarettes per day is common among people not ready to quit (Reid et al., 2019) and meta-analyses demonstrate nicotine replacement therapy (NRT) aided reduction approximately doubles the odds of cessation for smokers initially unmotivated to quit (Lindson-Hawley, Hartmann-Boyce, et al., 2016; Moore et al., 2009; Wu et al., 2015). Of note, though the use of NRT and other pharmacotherapies remains low (Gravely et al., 2021), the US Food and Drug Administration (FDA) has changed labeling requirements for NRT to allow use before quitting cigarettes (i.e., pre-quit NRT) (FDA, 2013). Some NRT-aided reduction interventions have been demonstrated to increase QAs among people initially unmotivated to quit smoking (Carpenter et al., 2004; Lam et al., 2015) while others have not (Cook et al., 2021; Engle et al., 2019). Importantly, the content of reduction-based interventions appears to vary

substantially (Lindson, Klemperer, et al., 2019) and the evidence of their effectiveness on increasing QAs among people not ready to quit tobacco has not been synthesized.

In addition to NRT, other pharmacological interventions could promote QAs among people who are not ready to quit smoking. Varenicline is an effective smoking cessation medication (Cahill et al., 2016), with mixed results in one large multi-site trial of smokers not ready to quit (Hughes, Rennard, Fingar, Talbott, et al., 2011). Electronic cigarettes are popular (Ali et al., 2020; Cornelius et al., 2020) and effective smoking cessation aides (Hartmann-Boyce, McRobbie, et al., 2021; Wang et al., 2021), and thus could also be effective in promoting QAs among smokers not ready to quit (Kasza et al., 2021). Finally, reduced nicotine cigarettes is a proposed policy intervention that has been demonstrated to decrease combusted tobacco use among smokers who are not ready to quit (Donny & White, 2021), though the effects on QAs per se has not been systematically reviewed.

The prior systematic reviews on interventions commonly used for people not ready to quit tobacco focus on a single treatment (i.e., motivational interviewing or reduction) and either do not test QAs as an outcome or do not limit their analysis to people who were not ready to quit at baseline. In this systematic review, we synthesized the existing research across a range of interventions to induce QAs among people initially not ready to quit tobacco (pre-registered review within PROSPERO, ID: CRD42020179363).

Methodology

Our pre-specified inclusion criteria were as follows: (a) the article reported the proportion of participants who made a QA (of any duration) as an outcome; (b) the study was a randomized trial that allowed for between group intervention comparisons; (c) all included participants were regular tobacco users (including either combustible or smokeless tobacco) at baseline; (d) all analyzed participants were identified as unwilling, unmotivated, not planning, or not ready to quit at baseline (as defined by study); (e) all included participants were adults; and (f) the article was published in English.

We searched PubMed, Embase, Cochrane CENTRAL, PsycINFO, and our personal libraries for articles that met criteria above. See Supplement 1 for a complete search strategy. Broadly, our search strategy included terms related to 1) tobacco use, 2) being unmotivated to quit, and 3) making a QA. Given the wide range of possible interventions to induce QAs, we did not include terms specific to tobacco treatment interventions (e.g., NRT, motivational interviewing, reduction counseling, etc) because doing so would have either further restricted our search to known interventions or required reviewing the entire body of tobacco treatment literature, which was not feasible in this review. Database searches queried all database fields, including title, abstract, and key words, in articles in press or published in English up to September 10, 2021.

First, we divided the resulting articles between two pairs of authors (including Klemperer, Streck, Su, or West) who each read the abstract and title of each reference for exclusion. References were excluded upon mutual consent by both reviewers. Second, these same pairs of authors then read the full text of the remaining articles and assessed them against the eligibility criteria listed above. Disagreements were discussed between the authors until a consensus was reached.

Two review authors (including Klemperer, Streck, or Su) independently extracted data on study characteristics and outcomes for each of the remaining studies (Table 1). Our primary outcome was the proportion of participants in each condition who made one or more QAs using the study's definition of a QA. Whenever possible, we used data on the proportion of participants who reported a QA that lasted ≥24 hours but in some cases QAs were defined as lasting any length or no definition was provided (see Table 1). In the cases where QAs were reported at multiple time-points (Higgins et al., 2020; Klemperer, Hughes, & Callas, 2019), we used QAs at the longest follow-up. We also extracted and analyzed data on the proportion of participants who achieved abstinence using the most rigorous measure (e.g., sustained was preferred over point-prevalence and biochemically verified was preferred over self-report) at the longest follow-up. We chose to use the most rigorous measure of QA and abstinence

outcome reported at the longest follow up to remain consistent with the standard used in prior systematic reviews (Lindson, Klemperer, et al., 2019; West et al., 2005). In some cases, outcomes of interest were not reported in the manuscript text and were only available graphically and thus we obtained data from the graphs using Web Plot Digitizer software (https://automeris.io/WebPlotDigitizer).

Two review authors (including Klemperer, Streck, or Su) used the approach recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019) to independently assess the risk of bias for each included study. We assessed the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, and other risk of bias. We followed the Cochrane Tobacco Addiction Group guidelines regarding the assessment of blinding and assessed both performance and detection bias in pharmaceutical trials where blinding of the participants and providers was possible. However, where the intervention was behavioral, making blinding to the intervention impossible, we only assessed detection bias. We report the risk of bias for each included study in eTable 1 in Supplement 1.

Data Analysis

We grouped studies by intervention and meta-analyzed findings when ≥2 studies tested similar interventions. We chose to group studies by intervention type to reduce heterogeneity resulting from differences in the types of interventions and to improve interpretation of pooled findings. Whenever possible, we sub-grouped studies by comparison condition and conducted subgroup analyses when ≥2 studies tested similar interventions compared to similar comparison conditions (Higgins et al., 2019; Valentine et al., 2010). Effect sizes for studies with multiple intervention or comparison conditions were calculated and grouped according to intervention type. For example, a trial with two intervention conditions (e.g., reduction and motivational counseling) and a control condition (e.g., brief advice) contributed separate effect sizes to meta-analyses comparing 1) reduction counseling versus brief

advice and 2) motivational counseling versus brief advice. We used Mantel-Haenszel random-effects methods to combine risk ratios (RR) from individual studies and calculate pooled overall RRs with 95% confidence intervals (CI). An RR of greater than one is associated with an increased probability of making a QA or achieving abstinence, while an RR of less than one is associated with a decreased probability of the outcome occurring. We made the a priori decision to use a random-effects approach because interventions and comparators varied substantially between studies. The data used for meta-analysis are presented in Figures 2 through 4.

Two papers reported aggregate findings from large 2^4 factorial trials (Cook et al., 2021; Engle et al., 2019). In these cases, the authors provided unpublished QA and abstinence data separately for each of the 16 conditions and we aggregated conditions to analyze outcomes according to the previously described groupings for meta-analysis. One paper reported the aggregate findings from three randomized trials in distinct populations using separate randomization sequences (Higgins et al., 2020). Higgins and colleagues provided unpublished QA and abstinence data for each trial and we entered results from each trial separately according to the previously described groupings for meta-analysis. Given the risk for substantial heterogeneity between studies, we made the a priori decision to report pooled effects only when I^2<75%, consistent with Cochrane cutoff for "considerable heterogeneity" (Ryan & Hill, 2019) and because high heterogeneity can result in misleading pooled effects (Higgins et al., 2019). Finally, two authors (Klemperer and Lindson) used GRADEpro GDT (https://gradepro.org/) to assess six domains (study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias) to evaluate the certainty of evidence for each outcome (Ryan & Hill, 2019). Our ratings of the certainty of the evidence for pooled effects are reported in the text of the results. There were no deviations from our pre-registered protocol (PROSPERO, ID: CRD42020179363).

Results

Our searches identified 347 references from PubMed, 792 from Embase, 1,103 from Cochrane CENTRAL, 616 from PsycINFO, and 60 articles from our personal libraries (Figure 1). After removing duplicates (n=431), excluding articles based on titles and abstracts (n=2,034) and excluding full text articles during our screening process (n=416 plus n=12 excluded during data extraction), 25 trials remained. We excluded the majority (78.1%) of studies because they did not report the percentage of participants who made a QA as an outcome (see Supplement 2 for reasons for exclusion).

The 25 included trials were published between 2002 and 2021, included 8,902 participants (Table 1), and 84% (n=21) were conducted in the United States. The remaining four trials were carried out in the United Kingdom (Taylor et al., 2014), Switzerland (Etter et al., 2002), New Zealand (Walker et al., 2015), and China (Lam et al., 2015). Eight trials (32%) reported specifically that recruitment did not mention quitting cigarettes or used language to target people who were not interested in quitting cigarettes (Carpenter et al., 2003; Catley et al., 2016; Davis et al., 2011; Etter et al., 2002; Hughes, Rennard, Fingar, Talbott, et al., 2011; Klemperer, Hughes, & Callas, 2019; Krigel et al., 2017; Riley et al., 2002). One trial offered interested individuals a cessation option as a behavioral indicator of motivation and recruited only those who declined as indicative of individuals who were unmotivated to quit (Carpenter et al., 2004). Two other trials recruited individuals interested in quitting or reducing but excluded those who expressed interest in quitting during the screening process (Cook et al., 2021; Engle et al., 2019).

Most trials (64%) included participants who, at baseline, reported no plans to quit in the next month. Three trials assessed baseline motivation to quit on a scale of 0 (least) to 10 (most) and included participants who rated their motivation as <7 as individuals who were not motivated to quit smoking (Carpenter et al., 2021; Carpenter et al., 2020; Catley et al., 2016). Three trials included participants motivated and unmotivated to quit at baseline and analyzed outcomes separately among the subset of participants who were unmotivated to quit at baseline (Carpenter et al., 2021; Carpenter et al., 2020;

Kruse et al., 2020). One trial (Hatsukami et al., 2008) tested an intervention for smokeless tobacco use and the rest targeted cigarette smoking. The follow-up periods during which QAs were assessed ranged from 4 to 52 weeks and most studies (68%) defined QAs as an attempt to quit that lasted ≥24 hours. All but two trials reported abstinence in addition to QAs and most (64%) defined abstinence as self-reported or biochemically verified 7-day point-prevalence abstinence at the longest follow-up (Table 1). Overall, we judged 5 studies to be at a low risk of bias (Carpenter et al., 2011; Donny et al., 2015; Higgins et al., 2020; Hughes, Rennard, Fingar, Talbott, et al., 2011; Steinberg et al., 2016), 8 studies to be at unclear risk, and 12 studies to be at a high risk of bias (see eTable 1 in Supplement 1). Eleven of the 12 studies judged to be high risk were rated as such due to blinding bias in pharmacological interventions or detection bias in behavioral interventions.

Counseling Without Medication

Motivational Interventions (Figure 2A)

Study Characteristics. Eight trials tested motivational interventions without medication (Carpenter et al., 2004; Catley et al., 2016; Cook et al., 2021; Davis et al., 2011; Engle et al., 2019; Klemperer et al., 2017; Krigel et al., 2017; Steinberg et al., 2016). Four of these trials provided telephone or in-person counseling based on the US Public Health Service recommended "5Rs" motivational intervention in one of their treatment conditions (Carpenter et al., 2004; Catley et al., 2016; Cook et al., 2021; Klemperer et al., 2017). The 5Rs intervention includes identifying the 1) Relevance of smoking, 2) Risks of smoking, 3) Rewards of quitting, and 4) Roadblocks to success, and then 5) Repeating these messages (Fiore, 2008). Of note, Catley and colleagues (2016) modified the 5Rs to deliver health education without components of motivational interviewing (MI) (Miller & Rollnick, 2012). In a condition distinct from their 5Rs-based health education, Catley and colleagues (2016) also provided four sessions of motivational counseling based on components of MI and offered free medication to participants who set a quit date. Three of the four trials that tested interventions based on the 5Rs offered free NRT

(Carpenter et al., 2004; Cook et al., 2021) or the choice of varenicline or NRT (Catley et al., 2016) to participants who elected to receive cessation treatment or set a quit date. Three trials provided a single brief motivational intervention (Davis et al., 2011; Krigel et al., 2017; Steinberg et al., 2016).

Two trials tested motivational counseling as part of large 2^4 factorial trials (Cook et al., 2021; Engle et al., 2019). Engle and colleagues (2019) reported QA findings from a prior factorial trial (Cook et al., 2016), which included three bi-weekly sessions of motivational counseling based on MI followed by the option to receive an additional 6 weeks of motivational treatment and 8 weeks of cessation treatment (counseling plus NRT). More recently, Cook and colleagues (2021) tested quarterly 5Rs counseling calls as part of a factorial trial that also offered an additional 8 weeks of cessation treatment (counseling plus NRT) to all participants who decided to quit.

Quit Attempts. There was substantial heterogeneity when effects were pooled across eight studies of motivational interventions versus any comparison condition, as well as among the subgroup of three trials that compared motivational interventions versus no treatment (I^2>75%). Thus, these pooled effects are not reported. The pooled estimate for the five trials of motivational interventions versus active comparators (brief advice or other brief intervention) indicated some evidence that motivational counseling may increase QAs, but confidence intervals included the possibility of no difference between conditions (RR=1.2, 95% CI=0.97 to 1.4; I^2=11%; 1,027 participants). We judged the certainty of the evidence regarding the effectiveness of motivational counseling to be very low, given the high statistical heterogeneity and the fact that confidence intervals include both benefit and no effect of the intervention.

Abstinence. The pooled effect for the eight trials of motivational interventions versus any comparison were in favor of motivational interventions, though confidence intervals were relatively wide and included the possibility of no difference between conditions (RR=1.8, 95% CI=0.9 to 3.6; I^2=62%; 1,561 participants). The pooled effect for the subgroup of three trials of motivational

intervention versus no treatment is not reported due to high heterogeneity (I^2>75%). The subgroup analysis of the five trials of motivational interventions versus active comparators suggests a significant benefit of motivational interventions over brief advice or other brief interventions (R=1.8, 95% CI=1.04 to 3.1; I^2=0%; 1,027 participants). However, we judged the certainty of the evidence for this outcome as very low overall, given the overall moderate statistical heterogeneity and wide confidence intervals.

Reduction Interventions (Figure 2B)

Study Characteristics. Five trials tested interventions to reduce smoking in the absence of pharmacological treatment. Four of these compared reduction to no treatment or brief advice (Cook et al., 2021; Engle et al., 2019; Klemperer et al., 2017; Taylor et al., 2014). The fifth compared computerized to manualized reduction counseling and found no clear evidence of a superior effect of either intervention difference between the conditions with regard to QAs or abstinence (Riley et al., 2002). In three trials, participants received telephone counseling to cut down on cigarette smoking and were encouraged to set their own reduction goals over the course of the 4-week (Klemperer et al., 2017), 6-week (Engle et al., 2019), and one-year (Cook et al., 2021) treatment periods. As previously described, two of these trials offered additional cessation treatment to all participants (Cook et al., 2021; Engle et al., 2019). In two other trials, participants were encouraged to reduce by 50% during two weeks of computerized or manualized treatment (Riley et al., 2002) and during 12 weeks of exercise-assisted reduction counseling (Taylor et al., 2014). Counseling to reduce cigarette smoking included strategies to delay smoking and abstain in certain places (Engle et al., 2019), the development of smoking control skills (Cook et al., 2021), as well as timed reduction (i.e., progressively increasing time between cigarettes) and hierarchical reduction (i.e., cutting out the easiest cigarettes to give up first) (Klemperer et al., 2017; Riley et al., 2002; Taylor et al., 2014).

Quit Attempts. The pooled estimate indicated no clear evidence of benefit or harm from receiving reduction counseling compared to no treatment or brief advice (RR=1.0, 95% CI=0.7 to 1.4;

I^2=41%; 606 participants, four trials), although the confidence interval indicated imprecision. A subgroup analysis of the two trials of reduction versus no treatment yielded similar results (RR=1.0, 95% CI=0.7 to 1.3; I^2=0%; 132 participants). There was substantial heterogeneity between the two trials of reduction versus brief advice (I^2>75%) and thus the pooled effect is not reported. We judged the certainty of the evidence for the effectiveness of reduction in promoting QAs to be very low given the high risk of bias among included trials, the inconsistency of effects, and the fact that confidence intervals include both benefit and harm of the intervention.

Abstinence. Four trials investigating reduction also measured abstinence from tobacco use (Cook et al., 2021; Engle et al., 2019; Klemperer et al., 2017; Taylor et al., 2014). The pooled estimate showed no clear effect and resulted in wide confidence intervals that included possible benefit and harm of reduction interventions when compared to no treatment or brief advice (RR=1.3, 95% CI=0.5 to 3.2; I^2=53%; 606 participants). The subgroup of the two trials comparing reduction to no treatment yielded an effect in the direction of harm from reduction, though confidence intervals were also wide and included a possible benefit (RR=0.5, 95% CI=0.2 to 1.4; I^2=0%; 132 participants). In contrast, the subgroup of the two trials comparing reduction to brief advice indicated that significantly more participants randomized to receive reduction counseling achieved abstinence (RR=2.4, 95% CI=1.2 to 5.0; I^2=0%; 474 participants). The level of certainty of the evidence for reduction interventions' influence on abstinence was judged to be very low, given the overall moderate statistical heterogeneity and inconsistency between studies' findings.

Combined Motivational and Reduction Interventions (Figure 2C)

Study Characteristics. Two trials tested combined motivational and reduction interventions. In the previously described factorial trials, combined motivational and reduction counseling was provided for 6-weeks (Engle et al., 2019) or one-year (Cook et al., 2021) and all participants were offered additional cessation treatment if they expressed motivation to quit.

Quit Attempts & Abstinence. The pooled effects did not appear to indicate clear benefit or harm from motivational plus reduction counseling for QAs (RR=0.9, 95% CI=0.7 to 1.3; I^2=0%; 131 participants) or abstinence (RR=0.8, 95% CI=0.2 to 4.4; I^2=68%; 131 participants). We judged the certainty of this evidence to be very low for both QAs and abstinence given that both included trials were judged to be at high risk of bias and confidence intervals incorporate both benefit and harm of the intervention.

Behavioral Activation and Other Counseling (Not Reported in Figures)

In one of the previously described factorial trials, Cook and colleagues (2021) tested behavioral activation alone (n=36 participants), behavioral activation with 5Rs counseling (n=37 participants), behavioral activation with reduction counseling (n=39 participants), and behavioral activation with 5Rs and reduction counseling (n=35 participants) over the course of one year. These interventions resulted in 47%, 43%, 41%, and 37% of participants in each respective condition making a QA as well as 6%, 3%, 13%, and 9% achieving abstinence. In contrast 49% made a QA and 17% achieved abstinence in the no treatment control condition (n=35 participants). Given the differences between this trial's interventions and the interventions of other included studies, we did not combine or meta-analyze these conditions.

Medication Alone and Medication with Counseling

NRT Alone (Figure 3A)

Study Characteristics. Six trials tested NRT compared to no NRT (Carpenter et al., 2011; Carpenter et al., 2020; Cook et al., 2021; Engle et al., 2019; Etter et al., 2002; Kruse et al., 2020). One large trial compared written material with versus without NRT sampling (i.e., a free take-home bag containing a 2 week supply of patches and lozenges) in a primary care setting (Carpenter et al., 2020). In this trial, Carpenter and colleagues (2020) recruited participants with a range of motivation to quit and conducted sub-analyses examining participants with low motivation to quit at baseline. Another large trial mailed 6 months of NRT with a booklet on reasons and strategies to reduce cigarette consumption

(Etter et al., 2002). As part of separate factorial trials, Cook and colleagues (2021) tested up to a year of NRT mini lozenges compared to no treatment and Engle and colleagues (2019) reported findings from a test of 6 weeks of NRT patch, NRT lozenge, or both products combined compared to no treatment. Two trials compared NRT plus behavioral treatment versus behavioral treatment alone (Carpenter et al., 2011; Kruse et al., 2020). Carpenter and colleagues (2011) compared counseling to promote practice QAs with versus without 6 weeks of NRT lozenges in a large national trial. Kruse and colleagues (2020) recruited participants with a range of motivations to quit and reported findings separately among those with low motivation at baseline. Two of the four trial arms compared 2 weeks of NRT plus text messages versus text messages only and thus isolated the effects of NRT alone. The other two arms compared NRT alone versus brief advice to quit (Kruse et al., 2020).

Quit Attempts. When pooled across all six trials, NRT increased QAs compared to no NRT or brief advice (RR=1.1, 95% CI=1.02 to 1.3; I^2=0%; 2,568 participants). The pooled effect remained the same in a sensitivity analysis that excluded the two conditions in Kruse and colleagues' trial (2020) that compared NRT to brief advice to quit. We judged the certainty of the pooled findings across all six trials to be moderate given that four of the six included trials were judged to be at a high risk of bias.

Abstinence. The pooled effect from all six trials suggested a possible benefit of NRT without counseling compared to no NRT, but confidence intervals also included the possibility of no effect (RR=1.2, 95% CI=0.9 to 1.5 I^2=0%; 2,568 participants). Findings were identical in a sensitivity analysis where the two conditions in Kruse and colleagues' trial (2020) that compared NRT to brief advice were excluded. These findings were judged to be at a very low certainty given the imprecision of the confidence intervals and the fact that four of the six included trials were judged to be at a high risk of bias.

NRT with Reduction Counseling (Figure 3B)

Study Characteristics. Four trials tested NRT with counseling to reduce cigarette smoking (Carpenter et al., 2003; Carpenter et al., 2004; Cook et al., 2021; Engle et al., 2019). One trial offered participants their choice of NRT for 4 weeks and provided a goal of 50% reduction in cigarette smoking (Carpenter et al., 2003). A subsequent trial provided participants with their choice of NRT for 6 weeks and encouraged participants to set their own reduction goal (Carpenter et al., 2004). Finally, both of the previously described factorial trials included conditions testing NRT plus reduction and offered all participants additional cessation treatment if they decided to quit (Cook et al., 2021; Engle et al., 2019).

Quit Attempts & Abstinence. There was substantial heterogeneity when the effects on QAs were combined across the four trials, and thus pooled effects are not reported. With abstinence as the outcome, the pooled effect across all four trials was in favor of NRT-aided reduction versus control conditions, but confidence intervals were wide and included the possibility of harm from NRT-aided reduction (RR=1.6, 95% CI=0.6 to 4.3; I^2=72%; 691 participants). A sensitivity analysis removing the one study that compared NRT with reduction counseling to brief advice rather than not treatment (Carpenter et al., 2003) resulted in substantial heterogeneity (I^2>75%). We judged the certainty of this evidence to be very low for both QAs and abstinence given the high risk for bias among included trials, imprecision (i.e., wide confidence intervals), and high statistical heterogeneity.

NRT with Motivational Counseling (Figure 3C)

Study Characteristics. The two previously described factorial trials included conditions testing the combination of NRT and motivational counseling. Cook and colleagues (2021) compared NRT mini lozenges plus 5Rs counseling versus no treatment over the course of one year. Engle and colleagues (2019) compared three NRT conditions (patch, lozenge, and patch plus lozenge) in combination with motivational counseling versus no treatment. Both studies offered additional cessation treatment to any participant who expressed interest in quitting.

Quit Attempts & Abstinence. The pooled effect indicated no evidence of a clear harm or benefit of NRT plus motivational counseling in promoting QAs (RR=1.1, 95% CI=0.8 to 1.4; I^2=22%; 200 participants, two trials). With regard to abstinence, the point estimate favored no treatment, but interpretation is limited by the fact that very few individuals achieved abstinence and the resulting confidence intervals were wide (RR=0.5, 95% CI=0.2 to 1.3; I^2=0%; 200 participants, two trials). The certainty of the evidence for both outcomes was judged to be very low given that both included studies with a high risk of bias and the confidence intervals were imprecise.

NRT with Reduction & Motivational Counseling (Figure 3D)

Study Characteristics. Three trials tested NRT with both reduction and motivational counseling. One large trial provided 8 weeks of participants' choice of NRT with instructions to reduce to quit plus 5Rs counseling to increase motivation to quit (Lam et al., 2015). Of note, Lam and colleagues analyzed "hardcore smokers" (i.e., participants who smoked 15 cigarettes/day and had no prior history of QAs) and "non-hardcore smokers" separately and found NRT with reduction and 5Rs counseling increased QAs among "hardcore smokers" but not among "non-hardcore smokers." In addition, half of participants in the NRT condition received brief intervention to increase adherence to NRT (Lam et al., 2015). The two previously described factorial trials also included conditions that tested NRT with reduction and motivational counseling. Specifically Cook and colleagues (2021) tested NRT mini lozenges in combination with reduction and 5Rs counseling while Engle and colleagues (2019) examined reduction and motivational counseling plus one of three types of NRT (patch, gum, or patch and gum combined) in three separate conditions.

Quit Attempts & Abstinence. The pooled effect for all three trials found no clear evidence for the superiority of the intervention or control conditions for QAs (RR=1.0, 95% CI=0.7 to 1.4; I^2=68%; 1,353 participants) or abstinence (RR=0.8, 95% CI=0.3 to 2.3; I^2=69%; 1,353 participants). Findings from a sensitivity analyses removing the one study that investigated brief advice as the comparator (Lam et al.,

2015) favored no treatment for QAs and abstinence but interpretation is limited by wide confidence intervals for both outcomes. Overall, the certainty of this evidence was judged to be very low given that included studies had a high risk of bias, there was moderate to high statistical heterogeneity, and confidence intervals were imprecise.

Varenicline (Figure 3E)

Study Characteristics. Three included trials tested varenicline among participants not ready to quit smoking (Carpenter et al., 2021; Hughes, Rennard, Fingar, Talbot, et al., 2011; Steinberg et al., 2018). One multi-site trial randomized participants to receive 2 to 8 weeks of varenicline versus placebo plus four brief reduction counseling sessions (Hughes, Rennard, Fingar, Talbot, et al., 2011). Another trial randomized participants to receive 28 days of varenicline versus placebo in addition to weekly counseling (Steinberg et al., 2018). Counseling consisted of three sessions to achieve a 50% reduction in smoking and a fourth session consisting of an adaptation of motivational interviewing to quit smoking (Steinberg et al., 2018). Finally, a recent pilot study recruited participants both motivated and unmotivated to quit at baseline, provided brief advice to quit plus 2 to 4 weeks of varenicline or no medication, and reported results separately among participants who were unmotivated to quit at baseline (Carpenter et al., 2021).

Quit Attempts. The pooled results across the three trials (only including participants unmotivated to quit) indicated that varenicline increased QAs more than no varenicline or placebo (RR=1.4, 95% CI=1.1 to 1.7; I^2=0%; 320 participants). The positive effect for varenicline remained in a sensitivity analysis excluding the trial that did not use a placebo-controlled comparison condition (Carpenter et al., 2021). We judged the certainty of the evidence regarding QAs to be low due to imprecision, given the small number (i.e., <100) of individuals who made a QA.

Abstinence. Two trials compared varenicline to no treatment (Carpenter et al., 2021) or placebo (Hughes, Rennard, Fingar, Talbott, et al., 2011). Pooled results indicated varenicline increased

abstinence (RR=2.3, 95% CI=1.1 to 4.6; I^2=0%; 267 participants) more than no varenicline. Similar to QAs, we judged the certainty of the evidence regarding abstinence to be low due to imprecision.

NRT with Behavioral Activation and Other Counseling (Not Reported in Figures)

In one of the previously described factorial trials, Cook and colleagues (2021) examined NRT mini lozenges in combination with behavioral activation (n=37), NRT, behavioral activation, and 5Rs counseling (n=35), NRT, behavioral activation, and reduction counseling (n=36), and NRT, behavioral activation, reduction, and 5Rs counseling (n=37) over the course of one year. These interventions resulted in 49%, 57%, 33%, and 49% of participants in each respective condition making a QA as well as 11%, 23%, 3%, and 5% achieving abstinence. In contrast 49% made a QA and 17% achieved abstinence in the no treatment control condition (n=35). Given differences between the interventions investigated here and those investigated in other trials, we did not meta-analyze trials of NRT with behavioral activation and other counseling.

Very Low Nicotine Content Cigarettes (Figure 4)

Study Characteristics. Four studies compared 6 to 12 weeks of very low nicotine content (VLNC) versus normal nicotine cigarettes (Donny et al., 2015; Higgins et al., 2020; Tidey et al., 2019; Walker et al., 2015). Donny and colleagues (2015) randomized participants to smoke cigarettes containing 0.4 mg/g nicotine, 0.4 mg/g nicotine + high tar, 1.3 mg/g nicotine, 2.4 mg/g nicotine, 5.2 mg/g nicotine, 15.8 mg/g nicotine (which is consistent with commercially available cigarettes), or the participants' usual brand cigarette for 6 weeks and reported QAs and cessation at follow-up, four weeks after study cigarettes were discontinued. Higgins and colleagues (2020) conducted three parallel randomized controlled trials among (a) adult women of socioeconomic disadvantage, (b) adults with opioid use disorder, and (c) adults with affective disorders. In each trial, participants were randomized to smoked cigarettes containing 0.4 mg/g nicotine, 2.4 mg/g nicotine, or 15.8 mg/g nicotine. Quit attempts and cessation were reported at a 4 week follow-up after study cigarettes were discontinued and QAs were

also reported separately during the study period. Tidey and colleagues (2019) randomized participants with severe mental illness to smoke 0.4 mg/g nicotine cigarettes or 15.8 mg/g nicotine cigarettes for 6 weeks and reported QAs four weeks after study cigarettes were discontinued. Walker and colleagues randomized participants to smoke 0.7 mg/g nicotine cigarettes or usual brand cigarettes for 12 weeks and reported QAs and cessation during the study period when participants had access to study cigarettes. In addition to the trials of VLNC cigarettes described above, another small trial provided all participants with NRT and compared a gradual transition from normal nicotine (15.8 mg/g) to VLNC (0.4 mg/g) cigarettes versus a gradual reduction in number of normal nicotine research cigarettes and found no difference in ≥24 hour QAs or abstinence between conditions (Klemperer, Hughes, & Callas, 2019).

Quit Attempts. Outcomes were entered separately for each of the three trials in the study conducted by Higgins and colleagues (2020) because the trials used separate randomization processes. Thus, six trials from four reports contributed to the QA outcome (Donny et al., 2015; Higgins et al., 2020; Tidey et al., 2019; Walker et al., 2015). There was substantial heterogeneity between trials of VLNC vs normal nicotine cigarettes (I^2>75%) and thus the pooled effect for QAs is not reported. Heterogeneity remained high (I^2>75%) in a sensitivity analysis where Walker and colleagues' trial (2015) was excluded and the pooled effect limited to the trials that reported QAs during follow-up, after study cigarettes were discontinued. Of note, Higgins and colleagues (2020) reported a greater proportion of participants assigned to smoke VLNC versus normal nicotine cigarettes across all three trials made a QA during the study period when participants had access to the study cigarettes (OR=6.0, 95% CI=1.7, 20.7).

Abstinence. Five trials from three studies compared abstinence between VLNC vs normal nicotine cigarettes (Donny et al., 2015; Higgins et al., 2020; Walker et al., 2015). The pooled effect did not provide any clear evidence of a benefit or harm of the intervention, as confidence intervals were wide (RR=1.5, 95% CI=0.7 to 3.2; I^2=19%, 1,052 participants). Findings were similar in a sensitivity analysis when Walker and colleagues' trial (2015) was excluded and the pooled effect was limited to

trials that measured cessation at follow-up, after study cigarettes were discontinued. We judged the certainty of the evidence as low because of the infrequency of outcome events.

Intervention for Smokeless Tobacco Use

The only trial to test an intervention for smokeless tobacco users (Hatsukami et al., 2008) provided participants in both conditions with eight brief weekly in-person counseling sessions to increase motivation to reduce, identify barriers to reduction, and problem solve. Participants in the active condition were also provided tobacco free snuff to help them reduce (Hatsukami et al., 2008). Hatsukami and colleagues (2008) found reduction with tobacco free snuff increased the proportion of participants who attempted to quit smokeless tobacco (34%) in comparison to reduction alone (15%; p=.03). The difference in biochemically verified 7-day point-prevalence abstinence at the 12-week follow-up (tobacco free snuff + counseling=19% versus counseling only=11%) was not statistically significant.

Discussion

The 25 trials included in this review included tests of motivational counseling, reduction counseling, NRT, varenicline, and VLNC cigarettes as means to induce QAs among individuals who were not ready to quit tobacco. There was substantial variability between interventions, and thus, our findings primarily serve as a description of the research on treatments to induce QAs among adults who are not ready to quit tobacco.

Most included trials tested medication to induce QAs. The three trials that tested varenicline found relatively consistent positive effects, demonstrating the potential benefit to use of this medication among smokers not ready to quit. Nicotine replacement therapy (NRT) alone increased QAs but NRT with counseling did not. Prior reviews generally found that NRT-aided reduction approximately doubled the likelihood of sustained abstinence among adults initially not ready to quit (Moore et al., 2009; Wu et al., 2015). In these prior reviews, it was unclear whether cessation findings were due to the

interventions' effectiveness in promoting QAs, conversion of QAs to quit success, or both. Our review focused explicitly on initiating QAs and found a small benefit to NRT alone but no clear benefit of NRT in combination with reduction or other forms of counseling. Importantly, interventions included in this review varied substantially in terms of the amount and type of NRT as well as in counseling content and duration. Future experimental research is needed to identify the effective components of NRT-aided counseling interventions to induce attempts to quit smoking.

There was no clear evidence that motivational counseling or reduction counseling increased QAs or abstinence in comparison to no treatment or brief advice to quit. Motivational counseling was the most common non-pharmacological intervention tested among smokers who were not ready to quit and included the USPHS recommended "5Rs" intervention (Fiore, 2008), a single brief motivation based intervention, and multi-session motivational counseling. Importantly, motivational counseling inherently focuses on *why* to quit smoking. In contrast, reduction interventions inherently address *how* to quit smoking, which a recent network meta-analysis found to be a more effective approach for tobacco treatment counseling interventions (Hartmann-Boyce, Livingstone-Banks, et al., 2021).

Reducing cigarettes per day is common (Reid et al., 2019), suggesting this may be an acceptable approach to individuals who find quitting unacceptable. Discrepancies between reduction trials' findings in this review could be due to the variability between interventions, including the magnitude and duration of reduction and the extent to which the counseling emphasized reducing to quit versus reducing as an alternative to quitting. Prior research has also found inconsistent effects from reduction-based interventions among smokers who <u>are</u> motivated to quit (Lindson, Klemperer, et al., 2019; Lindson et al., 2020). However, there is some evidence to suggest that, a greater magnitude of reduction in smoking is associated with QAs (Klemperer, Hughes, & Naud, 2019) and cessation among smokers not ready to quit who received a reduction intervention (Lindson-Hawley, Shinkins, et al., 2016).

Limitations and Considerations

The majority of tobacco intervention studies (>75%) identified in our literature search were excluded because they did not report QAs as an outcome. Initiating an attempt to quit is an inherent and distinct component of tobacco cessation and future research would be much benefitted by reporting QAs as an outcome. Assessing QAs is important to identify incremental movement toward cessation and detect whether tobacco interventions affect quit initiation, maintaining abstinence, or both. A systematic search of the entire tobacco literature was not feasible and thus studies that did not adequately describe their population as being unmotivated or not ready to quit may have been missed. There was substantial heterogeneity between included studies and thus we were limited to a series of small meta-analyses, resulting in pooled estimates with moderate to very low certainty. This means that the interpretation of the effects reported here are likely to change as further evidence emerges. We did not have an adequate number of studies in any given meta-analysis to adequately test for asymmetry or detect publication bias (Sterne et al., 2011). The issue of engaging individuals in treatment who are not ready to quit was not addressed in this review. Low treatment engagement is common (Shiffman et al., 2005; Soulakova & Crockett, 2017) and could have contributed to the inconsistent effects in this review, especially among medication trials. The included trials of VLNC cigarettes were designed to examine reduced nicotine cigarettes as a regulatory intervention and not as treatment to promote quitting. Thus, findings could differ in research that utilizes VLNC cigarettes as part of a smoking cessation intervention. Though we were unable to find studies examining e-cigarettes to promote QAs among smokers not ready to quit, prior systematic reviews demonstrate that e-cigarettes can be used to increase cessation among smokers motivated to quit (Hartmann-Boyce, McRobbie, et al., 2021; Wang et al., 2021).

Future research that biochemically verifies smoking status and compares interventions to time-matched active or usual care comparison conditions are likely to reduce bias and be most useful in identifying treatments for smokers not ready to quit. Though we found varenicline and NRT both increased QAs, our certainty in these findings was low to moderate and thus future research on both

medications is warranted. There is a notable paucity of research on interventions for non-cigarette tobacco, ENDS to induce QAs, and the use of VLNC cigarettes as cessation treatment for smokers not ready to quit and thus further research is needed on these topics. Finally, all intervention trials for smokers not ready to quit should assess 24-hour QAs.

Conclusion

One cannot succeed in smoking cessation if one does not try to quit. Importantly, most US adults who smoke do not plan to quit in the near future and thus interventions designed to induce QAs are needed to increase the prevalence of smoking cessation. Our findings demonstrate that even patients not motivated to change can benefit from treatment and make positive smoking behavior change by initiating a QA. These results support national guidelines which recommend cessation treatment be offered to all smokers, regardless of their interest in quitting (Krist et al., 2021). Pooled estimates from this review suggest varenicline and NRT may be particularly promising interventions to promote QAs and thus should be considered in future guidelines for treating smokers not ready to quit. However, there was substantial heterogeneity among interventions and evidence was insufficient to conclusively support or refute the effectiveness of any single modality. While it is important that tobacco treatment guidelines include interventions for smokers who are not ready to quit, the optimal treatment (or treatment combination) for this population remains unclear. Thus, findings from this review serve as a description of existing interventions and illustrate the need to improve treatments to induce QAs among individuals who use tobacco and are not ready to quit.

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